Oncology Corner Le coin de l'oncologie

Chemotherapy: Managing side effects and safe handling

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Chemotherapy is a common treatment modality in many veterinary cancer patients in addition to surgery and radiation therapy. Cytotoxic drugs can lead to complete remissions for some disseminated cancers (lymphoma, for example), be effective in decreasing tumor size, and may prolong life in many other types of metastatic cancers, such as osteosarcoma. The choice of specific therapies depends on tumor type (what it is), histologic grade of the tumor (how aggressive it is), stage of disease (where it is), and the patient's (but mainly the pet owner's) tolerance for the side effects of the various treatments. Most of the chemotherapy protocols designed for veterinary patients have a $< 5\%$ incidence of severe, life-threatening complications (1). Most veterinary chemotherapy patients enjoy a good quality of life while on therapy. This article will discuss some of the side effects associated with chemotherapy in veterinary patients and how to effectively treat them. In addition, an overview of chemotherapy safety for both patient and veterinary staff will be discussed.

Veterinarians engaging in the practice of oncology require a thorough knowledge of the effects and toxicities of anticancer drugs. Since these agents possess the lowest therapeutic indices of any class of drugs, they produce frequent and predictable multi-system toxicities. Anticipation of possible complications and close attention to subtle clinical signs are essential to assure early introduction of prophylactic or therapeutic supportive care. Toxicities are most often acute, but chronic or delayed effects do occur. An index of suspicion for these problems is essential for their diagnosis. The Veterinary Cooperative Oncology Group (VCOG) has published a document outlining the common terminology criteria and providing a grading scale for adverse events following chemotherapy (2).

Simply put, chemotherapy kills rapidly dividing cells. Unfortunately chemotherapy drugs do not differentiate between killing tumor cells and normal cells. Thus, the general side effects of chemotherapy include bone marrow suppression, gastrointestinal problems (nausea, vomiting, diarrhea), and alopecia (1). However, in addition to the general side effects seen, specific side effects can result from certain drugs, for example, doxorubicin (cardiotoxicity) and cisplatin (fatal pulmonary edema in cats, renal toxicity in dogs).

The most common toxicity associated with chemotherapy is bone marrow suppression. Bone marrow cells divide rapidly because there is normally a high growth fraction in this tissue. Since activity of most anticancer drugs is greatest in tissues with a high growth fraction, the bone marrow is a prime target. The clinical result of myelosuppression is varying degrees of peripheral blood cytopenias. The rate of disappearance of individual blood cell lines correlates with the life span of that line. For example: RBC — 120 d (dogs), 70 d (cats); platelets — 5 to 10 d; granulocytes — 4 to 8 h. Granulocytopenia (specifically neutropenia) usually occurs first and is most often followed by thrombocytopenia. Anemia is rare and usually only mild to moderate.

Neutropenia is usually the most serious and dose limiting cytopenia associated with chemotherapeutic drug administration. The nadir (time of the lowest neutrophil count) varies with individual drugs. Nadirs in small animals occur between 5 to 10 d — standard practice is to run a complete blood (cell) count (CBC) at 7 d post-chemotherapy administration in order to detect the nadir, though the nadir can be missed. It is important to note that some drugs have a delayed or second nadir at about 21 d (carboplatin, for example) (1). Neutrophil counts usually rebound from the nadir within 1 to 3 d. Immature granulocytes are an indicator for return of granulocytic activity. Animals with < 1000 neutrophils/μL are at an increased risk for sepsis and require close monitoring. Neutrophil counts $< 500/\mu$L (categorized as a grade 4 neutropenia) usually are associated with fever and sepsis (1). In addition to lower neutrophil counts, chemotherapy can result in gastrointestinal epithelial desquamation, and the combination of these factors can lead to increased opportunity for enteric bacteria to enter the circulation causing septicemia, with fewer phagocytic neutrophils to effectively clear the infection which can be life-threatening.

Treating the neutropenic patient

Oncologists have various cutoff values that they adhere to when deciding whether or not chemotherapy will be administered. This author's cutoff value is 1.5×10^9 cells/L (1500 cells/μL) for neutrophils and 75×10^9/L (75 000 cells/μL) for platelets. Animals with neutropenia (< 1500 cells/μL) that are afebrile and asymptomatic should have chemotherapy delayed for a few days to 1 wk based on the severity. A broad spectrum antibiotic should be administered for 5 d if the neutrophil count is less

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Figure 1. Chemotherapy agent drawn up in a sterile fumehood. Note that both gown and gloves are worn.

Figure 2. Once the chemotherapy agent is prepared, the syringe is placed in a labeled sealed plastic bag. This process prevents contamination of surfaces and provides a disposal for all used chemotherapy waste.

than 1.0×10^9 cells/L (1000 cells/μL). Chemotherapy may be restarted once the neutrophil count and platelet count have increased to the appropriate minimal cutoff level. Many oncologists will reduce the dose by 20% if there is a treatment delay; however, this author only reduces the dose when a grade 4 neutropenia has occurred. It is reported that when a dose is reduced by 20%, the efficacy of the therapy is reduced by 50% (3).

If the patient is neutropenic and febrile with or without clinical signs (such as vomiting, diarrhea, trembling, dehydration, weakness, lethargy) chemotherapy should be discontinued. In some cases, a fever may not be present but the patient has clinical signs. The patient should be hospitalized on intravenous fluids and antibiotics, such as ampicillin and enrofloxacin in combination, to cover both gram-positive and gram-negative bacteria (4). Other symptomatic support should be provided such as parenteral nutrition and anti-emetics such as Maropitant (Cerenia), Ondansetron (Zofran) and/or Metoclopramide (Reglan). If the patient is not responding to antibiotic therapy, blood cultures should be considered. Fever usually responds within 12 to 24 h.

Neutropenia cannot always be prevented; however, tactics such as monitoring CBCs weekly or at the time of the expected nadir, checking for occult infections such as in the urinary tract or skin prior to therapy, and reducing chemotherapy drug doses in patients that have previously shown extreme sensitivity to these agents may be helpful in reducing its occurrence. Controversy still surrounds the practice of administering prophylactic antibiotics to patients receiving chemotherapy. In one report from the human literature, a review was performed to assess the evidence for the effectiveness of oral prophylactic antibiotics to decrease bacteremia and infection-related mortality in oncology patients during neutropenic episodes (5). The study concluded that these antibiotics decreased gram-negative bacteremia and therefore infection-related mortality. No evidence of bacterial resistance to these antibiotics was reported. In the veterinary literature, the use of oral prophylactic trimethoprim/sulfonamide (TMS) was found to be beneficial for reducing multiple toxicities during chemotherapy with doxorubicin (6). Careful monitoring of the patient is recommended to address the possibility of potential resistance.

Gastrointestinal toxicity

Although most animals tolerate chemotherapy treatments very well, some animals will have gastrointestinal side effects such as vomiting, diarrhea, and/or decreased appetite. There may be various reasons for these side effects. There can be a direct stimulatory effect by the drug on the CNS vomiting center or chemoreceptor trigger zone (CRTZ). This vomiting will occur during or soon after drug administration and can last for 1 to 2 d (4). The usual culprit for this immediate vomiting is Cisplatin — the reason why an anti-emetic is typically given prior to its administration (1). Chemotherapy can also have an indirect effect secondary to drug induced gastrointestinal inflammation and damage. This damage usually occurs 3 to 5 d post treatment. Gastrointestinal side effects may range from mild, such as a day of inappetence and soft stool, to severe with protracted vomiting and bloody diarrhea leading to dehydration. Treatment is usually symptomatic. If the signs are mild, patients can be managed at home. Nothing per os (NPO) for a day followed by a bland diet is usually sufficient. Animals that are more severely affected may require hospitalization with IV fluids and anti-emetics.

Figure 3. Demonstration of chemotherapy administration – note gown, gloves, and mask.

Chemosafety

Many veterinarians in general practice are administering chemotherapy either on their own or with the guidance of a veterinary oncologist. Chemotherapy can be used in general practice provided the following: that biosafety rules are strictly adhered to by all personnel directly and indirectly involved with the patient and drugs, patient safety is a priority, and that the practitioner is knowledgeable about all aspects of the drug to be used prior to its administration.

Safety for you and your staff

Safe handling of chemotherapy drugs cannot be overemphasized! Safety protocols can be posted everywhere in a clinic but it is everyone's responsibility to understand and follow these protocols, otherwise, they are just written words on a piece of paper. To ensure your own safety and that of your staff, the best way to avoid unnecessary exposure to potential toxins is by using proper handling techniques. Chemotherapy exposure occurs three ways: aerosol, topical, and oral. To reduce or prevent exposure the following protocols are recommended:

1. Prepare chemotherapy drugs in a sterile fume hood (Figure 1). At the WCVM and other specialty clinics, this is a reasonable option but most veterinary practices do not have hoods. Therefore, a quiet room on a clean surface away from ventilation ducts is recommended. An approved chemotherapy mask, gown, and gloves must be worn while preparing chemotherapy agents. There are now commercially available closed systems that reduce the risk of aerosolization such as PhaSeal. At the WCVM, we have just started using this system to reduce the risk of exposure even further. In addition, all chemotherapy is placed in a sealed plastic bag after it is prepared to reduce contamination of surfaces (Figure 2).
2. Approved chemotherapy administration gloves are preferable to latex examination gloves that are not impermeable to chemotherapy agents. If chemotherapy administration gloves are not available, double gloving with latex exam gloves is acceptable. A nonabsorbent chemotherapy administration gown or, at minimum, a clean buttoned up lab coat should be worn during administration. A mask and protective eyewear should also be worn. This protective wear should be worn by both the "giver" and the "holder" (Figure 3).
3. No food or drink should be in the chemotherapy administration room. A refrigerator should be assigned for chemotherapy drugs only and food should never be stored in the same place.
4. Once you are finished administering the drug, all chemotherapy waste (syringe, IV catheter, bandages, etc) should be returned to the sealed plastic bag and disposed of with other Biohazardous Waste according to government regulations in your area and not thrown in a sharps container or garbage.
5. Because chemotherapy drugs are excreted in feces and urine, we advise clients to wear gloves when cleaning up after their pets for up to 48 h after drug administration and wash the area with diluted bleach. Presently there are no written guidelines that exist for the disposal of pet waste.
6. It is recommended that pregnant or nursing staff refrain from being involved with handling chemotherapy drugs and patient waste. If there are inquiries as to other individuals who may be at increased risk (immunocompromised), consider discussing the situation with a physician.
7. A pre-existing protocol should be in place (for example, spill-kit, emergency procedures) should a spill occur.

Safety for your patient

Regardless of the type of drug you are using, it is essential to know how to administer it (oral, subcutaneous, intramuscular, or intravenous) and once it is given what general and specific side effects may occur. For example, L-asparaginase is a safe and well tolerated drug when administered subcutaneously or intramuscularly. If given intravenously, L-asparaginase will result in a (potentially fatal) anaphylactic reaction (1). Another important example is cyclophosphamide, an alkylating agent that is effective against a wide range of tumors. A major side effect that may occur even after a single dose is sterile hemorrhagic cystitis. This side effect can greatly alter quality of life for a patient, thus, by taking simple precautionary measures such as administering cyclophosphamide with either prednisone or furosemide (1 mg/kg once), we can greatly reduce this problem (1).

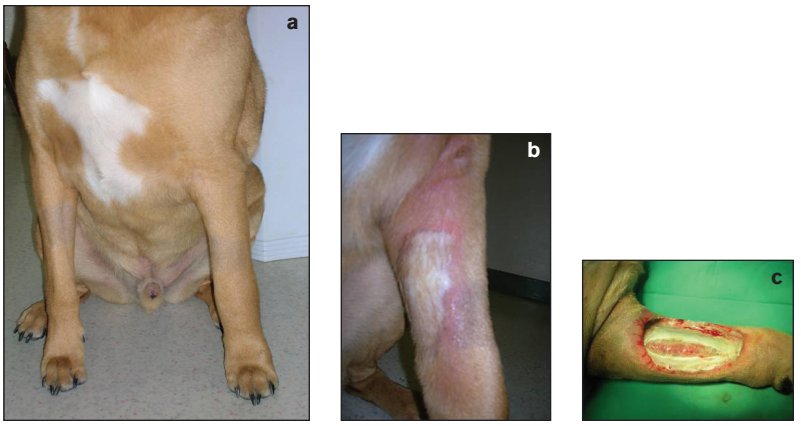

Figure 4a, 4b, 4c. A mixed breed dog receiving chemotherapy for Stage III lymphoma developed a severe reaction after extravasation of doxorubicin that was noted at the time of the infusion. Images of the left thoracic limb demonstrate the appearance of the lesions at (a) 6 days, (b) 10 days, and (c) 17 days post-infusion. An amputation of the affected limb was performed at 21 days postinfusion. The dog had a permanent draining tract after amputation and was euthanized shortly after.

Since most chemotherapeutics are administered intravenously, a well-placed catheter is essential. If the vein has been recently used, or if you have already damaged the vein in an attempt to place a catheter, go to a new leg. "Fishing" for the vein cannot be done as you are potentially putting microtears in the vessel with each "stick." This author always uses the jugular vein for taking blood samples and saves peripheral veins for chemotherapy administration. Having an indwelling catheter should prevent accidental extravasation of tissue irritants such as vincristine, vinblastine, or doxorubicin. Be sure to flush the catheter with 0.9% sodium chloride before and after administration of the chemotherapy drug.

If strict adherence to IV catheter rules occurs, extravasation can virtually be eliminated; however, accidents can still occur. If extravasation occurs with a mild/moderate vesicant such as vincristine or vinblastine, you should aspirate the drug out of the site if possible. Mark the area with an indelible marker so the affected area can be observed. Inflammation and edema can be reduced by applying warm compresses to the site for 10 to 15 min every 6 h for 24 to 48 h. Even though the resulting tissue damage can sometimes be significant, it rarely results in the loss of the limb.

However, if a severe vesicant like doxorubicin is extravasated, the resulting damage can be so severe that it may warrant amputation or even euthanasia of the patient (Figure 4) (1). If extravasation occurs, attempt to aspirate as much drug as possible. Do not flush the area with saline in an attempt to dilute the drug; this will only spread the drug further into the tissue. Place another IV catheter in a different leg and administer dexrazoxane (Zinecard) at 10 × the dose of doxorubicin (if the dose of doxorubicin was 20 mg, then administer 200 mg of Zinecard). The initial dose should be given within 3 h of extravasation and then again within 24 and 48 h. While no clinical trial has been reported for using this protocol, anecdotal reports in client-owned patients have shown that this approach works and has greatly lessened the severity of tissue damage. If dexrazoxane is not available, early surgical debridement can be done.

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